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Figur

F. å E 5 5 · 5 8 No. 东京 E 3 % 3 3 F X S 37 lys P. : . 15 13 5-3 E 3 ξ 2 3 3 % E ķ B 7 Į. Į 23 35 ह इ 35 E # 55 Fi ž ž ¥ ţ 京部 55 2 3 83 E ដូ 8 13 B इ दु 3 2 33 35 日 E รี 689 B 3 818 ध्र ध्र E a 37 35 84 3 5 X i 5:3 答言 £ 3 3.3 इ द 414 35 ¥ª 50 ខ្ម g 8 3 ¥ li ü 917 g £ 3 वृ । ឥ ij ង រ g g is is 片系 दिश a g 202 Į ኧ arg g E 517 B 3 Ę 3 g asm gle tyr 12 51 ירו ידו אלו אלר als les les oly ANC ANC GAG 1 ests asm gle : TAC ATT TAC TACT OF THE CAC OF 5731/1911 633 TG3 TAT C 91y ETP Cyc ' 5821/1941 val ser les les ile val דוכ אור פעד פוץ בני נים उस उस्ट भरा phe ile asp St. 18 Cy8 BE: phe leu 13 AT 915 1761/1163 5551/1851 5641/1881 1002/1009 6091/2031 1971/1818 5461/1921 5271,7091 1971/1765 6361/2121 8.9 4.5 653 [8 E ě 202 373 <u>y</u> XX ध्र 35 3 3 E 3 ğğ 3.7 £ 3 2 rhe r Ŗ 4 £ 24 2 ë ë The The 77.5 Jen <u>ع.</u>. 913 253 83 3 2 12 8 ŧ និនិ F # ti 5 6 Ë X E g हें से 38 38 EZ 1 3 ្រី ដឹ K 3 3 3 212 ម្តី មិ 8 3 ម្ភា E & १ ६ ¥ 8 5 E Ř ii Ęä 2 3 5 E A ន្តង E Z S 百节 11 ¥ % 臣出 以言 ð BR TAT Ban 13 GAT 350 8 5 3 3 § \$ 33 XIX 1:e ¥ ii 44 E 3 र्व श Ex \$ 1 र् रे che pro the lys 3.5 ğ 語語 E s 3 ă 35 द्री भित्र ង្ក हें हे ધુ phe ser leu asn ala a a a × 5 Į. ž g ğ ţ 3 Į 33 413 Ä ner and and and see als els els els 9 પુ SCG TAT TAN BLANCH CAC TET CAG ? phe ass ass ala, erp the and the tea मत क्या क्या ATT ANA TOC 11e 1ys ser THE TE 75 X5 75 ser thr ser क्ष्य स्थ ९८ ६८ मा 37. TAS 17. 13 אכני אבר פינר ery ile va! 1961/1885 5251/1751 5431/1811 5611/1871 1061/1015 5791/1931 1961/1665 5341/1781 6061/2021 521/184 Ŗ E. ANA OCT 1ys 9!y איז אא באא פאז פאז הזא ţ Pro 212 E EZ ង្គ ខ្ល g 돐 Ę 3 jle 91% ሯ Ž ઇ asn 51y ¥ ß યુ 25 7 F 15 g Jeu TX. 11e 设设 513 Z 175 25 5 K 밝얼 Ę 井 E ţ g X 23 设备 53 ATC HE ES हुनु g a \mathfrak{F} 917 EZ 3 8 हिं हैं हैं है 下品 ž g रूप्त EZ Į, なる 15 53 हुं हें l: a 35 हरी 片品 F. a 民員 3 :1 E 3 3 EF 517 13 13 g g 38 វូ ដូ 0:0 Kä). 13. 28. ns F ဒ္ဓ 4 4 R ť ij 33 5 F EB g z 8 8 t i ង្ក] S E 3 E E हें हैं gat 27 E F [: ţ glu pre net ala E 787 C a 3 Z 8 Į ż 3 5 E S כאכ כמכ כאכ זאד g שאם נכב אנב cyr lys pro lle \$581/1861 ala į TEC CAN CES ATG ş Ŗ ננ 7 eary pro esp tyr phe ser ala ser 5851/1951 esn OPA leu asp 3 5941/1981, TTC GTT TGT (ANG COC CCC (1) \$671/1891 TOT TCA TIT! Cys OPA phe 1 5761/1921 30 83 le pro asp म्म स्टब्स **然 校 好** क्ष दत्र मद STC ATC the val cys gin pre ser 45 EF 43 Se ti 1yr 140 vn \$221/1741 1081/1095 5491/1831 6031/2011 6:21/2041 6211/2071 6301/2101 36

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3 3 . **5** 3 Eš ¥ 5 8= Þ 1; \$ \$ 35 116 32 Ė E ß gly 以出 Ę 32 ğ 7 3.5 3 gly 110 SE E ţ ij ij g 5 ß ð Fig 3 5 ğ 3 E 917 Ş E phe E B 5 ध्रे द्व g E ठ्र g a Há At !! 3 S 3 3 ₹ 3 13 र्रे न ·8 \$13× E let leu 1 als K E ยี่ g ž R. A ¥ z Ę 919 917 E वि व Ę Ą į B ile val ile ser les ij **Q**)ec 8 gly E E E ŧ 3 £ £ ·y 3 7 Ş 감 ß g b ţ thr glu gly (ANA ACTO TOTAL אבי אדי אבא אבי אבי אבי זור פבים tro acc cor les the gly रेंद्र दूर द्य the pro 11e 54 H 85 als ser sis ATA ATC AAC בים איני בדד eso ele CAS STG ATC cly cly אר: מנא אר: אבני נבני אנא 11. CS 47. lie ile een 3 R 88 بعز جائ ह्म हर क let and phe ole asp 6721/2261 6991/2331 7621/2541 68:1/2271 1081/1361 1531/1651 6631/2211 1261/1921 1171/2391 7441/2481 5541/21E1 1351/2451 K Sly S z ä ST CT Te Te Te Te ä esr \$15 :17 1.X. ÿ 2 ¢1y aly ঠ্ נ<u>ל</u> ម្ភ 7 the cys 3 5 ធ្វ ğ 8 Z ₹ ţ 2 : 33 K **2** 2 X : 2) te 12 8 3 4 11. ţ g 917 E 44 ձ 2 Siy E 技艺 Ř.ÿ ţ XX = 1 979 £3 8 3 设备 4 3 5 3 3 BR g 光記 Fi 13 517 g 414 9-9 ţ į 百百 F Z 13= FE र्व हे 日二 下部 g 百計 뱑냋 र्ध व ₹ ¥ ١٤٠ 智智 35 aly 8 3 र्ध न 8 5 ह ह 3 % E I 4 8 35 917 E çly 7 ₹ ÿ ધુ 53 Ę ž E g g 3 % 4 13 g 1 ţ E g 4.3 ठ श 60C ACC COC CCA (91y the 51y 21a 6 6971/7291 TEC ANA ANC I sly ĭ F F P : ર્યુ Ē 3 . ys ğ ß Ë ş Ŀ glu tyr lys ser 6961/2121 Ą 以 § § Z ij y 1321/2441 AMC TEC AMA A 7141/2381 THG TCS TAX 2 Jeu ser OCH 2 70\$1/23\$1 505 305 305 Tes Art AM 1 2 g G ale giy ser ser che ביא דונ אים Š 32 55 日本 SP SP 3C 1C 3K 3K 高語 glu leu 91y ale gi 6781/2261 1231/2411 1591/2531 17171 6601/2201 6691/2231 7411/2471 1501/2501 217 6511 3 41) ţ 16. g 4 E 3 8 517 S * K R CTA TEA Low Lea 7 ţ 8.3 13.3 Ĭ; =: E S E & ีย 33 EZ B 51y 91y 3 5 Z Z 25.25 ٥. 1 a g ala 13 010 E 3 E g **5** 3 본걸 3 % 33 Ħ= ser ile leu'c 5 3 3 18 23:3 917 g H **\$ 8** ह्रि F. ğ 34 育 ž B なな 다 경 Ed Ř i 5,7 gly .5ly 38 g 23 ž Ę ş g g 1 हें है EZ EZ 35 支持 z g **5** 54 包貨 Fã ð 3 おれ . ţ 12 2 * £ 5 36.7 芦荟 R R ູບ pro いい 5 3 917 Ę 517 g ij ष्ठ 5.5 * 857 ધ્ર (2 F :: 3 33 Į į P.S 5 3 23 3 5 917 114 ş ð ¥ Ş B E 5 217 ¥ 2 \$ **5** الله برا Ä 员员 E . g ş 8 E Tr y Fig ET 91y 91y ; 1ys ary the 1201/2401 TEA TEC OCA 10PA Cya ala 17291/2431 917 11e phe esm 7021/234: XSA GGA TTG : ale leu 34 64 11e 1eu ser 7471/2691 773 Arrs Arr Fi B aly leu 74 111 ATK 色年日 פאל. אות St th स्ट स्टा स्टा स्त्र ख्य स्त सु भू ह lee glu יולא אלני Set ser 6481/2161 1222/1999 6751/2251 6941/2282 1121/2372 1383/2461 7 ij 5 Ė 5. 36. Ę 80

रह न E W g z 5 5 ร่ ₹Ÿ 1 is s e c 83 8 1 13 3 e a g ţ, þ 3 g 4 5 T 3 BB K 3 ¥ Þ 3 हैं में ¥ A T E Fig प्रश] g प्रम वस E 끍 7 ž f ध्र 3 ğ t ţ 出 7 ğ প্ত 京芸 367 Ser K ال ا 8 8 g 3 630 ष्ट्र 2 pro 8 g 8 g 5 8 ð 674 3 ij OPA g pro g 5 5 416 ð Çly F ٤ 0:0 171 ß ខ្ជ ß 414 3 G g 3 ij 216 ľ ţ ध्र 3 ¥ ğ g 1 g Ä ध्र র্ 3 Ę 5 E 917 E 3 B ğ E 2 ğ 3 asp CAT 7 13 91y cya ply glu 8251/2751 3 3 87 3 2 its gly his gly val pro asn ANT GAN TOTO COCT ANG OCC ADC ANA
Ilys als ser lys E lay rile els gas g Sire and out Sire ß 300 8 Ŋ ţ Ber t 7 Š ב क्षत क्षत क्षत 30 CC 63 अर द्रम् क्ट गर क्ट glu ser るないる עני עני יומנ CSC 151 ASC tre eve erre क्र क्र क्र 好好好 ser ser OPA פעם דינם מזא कर तत अठ tep les lys CH M CH ser pro thr clu lee val 1961/1661 8071/2691 8161/2721 3521/2841 8341/1781 8<31/2811 8701/2901 3791/29jì 8611/2871 1962/1/59 9681/2961 3 3 250 687 1 57 Te न्त E Ę ទូ ព្រ ij 0.0 Ť 11e Ė 뢽 ð 11. ğ 3 2 Ř 1: £ 3 2 3 E val ķ Ë ,K Ë 17. Ľ Stt 2 % 3 c Ju **35** E s ង រ 7. alc Š £ & Ę ij S ť 3 ₹ <u>₹</u> ร 3 15 87: 2:T. 99. 11e 1 Į. S 43 g 3 8 5 दिन तुर बीब जिस ğ ij g H ¥= 17 6 E 3 長 第 32 1 8 . <u>F</u> 計 e a Ŗ. ţ j g -1 र भ Ä 7. 8 3 270 K 百十 ij 83 なる 3 53 ន្តន g & 6.3 ध्र भ्र B ş ij ă Ş t 3 300 ķ ð Ę 另刻 E 35 K lev ile als his sia val ध्र B G Ş 3 gle ij 1 E ξ 8.13 7,75 ğ ß 3 1 .<u>శ</u> B 3 ધુ K 3 น ser als pro leu the lew glu ale pro ser Sly ret ĮΞ tyr pro gly phe S S :: g Ę 3 t 1 nts cad ato ¥ r. ery ser les the 3 g g 14: B ţ র্ ğ 3 ğ אל אנו אנו esp ile lys ser ary glu אטו ככם פרא ele pro क्र शिष्ट क्र क्ष त क्ट कि क SEC ATA ACE 51y 11e ch स्त हर व्य ति क्ष क्ष なるな तर भेष्र द्व श्री हर हो। gle er 节节 Sys 023 **8** 8 8 ler ec 1961/2621 8041/2661 6131/2721 8221/2741 1772/1169 8451/2931 8761/2921 8401/2801 1981/2551 8581/2861 6671/2891 8851/2951 E 919 £ 212 3 ¥ ונה Ę รู ξ ध्र द्व Ä દુ Jeu pro 3 713 0 E ğ ផ្ត R leu ser 臣员 ħ 2 4 Fig इंड g ŭ ä ä Į. 36 ႘ွ 4 र्व म E E Z 11 ATA ŧ E ğ 1 প্ত 917 B K 35 7 110 OH 0110 ři ë D'a ij ¥ 7 g8 ß 83 g 듼 ŧ 8 6 ន្ត និ র শ্র 7 Fa t FH 곉 F מום 8 8 3 ጀ t Få E 16:3 វួ ii. Ph. Į: 8 C 83 Kä ह इ E į E = 经音 X 9 716 8 13 5 3 3 24 TXT <mark>አ</mark> ţ 910 ğ S is P.Z ð なが 375 ş š į 13 7 Fig. ង 3 7 818 pro 3 467 35 ţ ğ \$13 g 917 3 Ê รี 5 pro Þ 8 F g g 3 អ្ន 84 12 133 랷 ķ ሯ ij 3 E ጀ E 12 3 8 ž ¥ % អូ K ij the lee giu gly E 5 ¥ 3 ช 53 吳島 g asp les his St 75 SC tyr aly less ile val ile באר הבה הבה B 15 3 his val ser THE PER SE 12 23 ביד דב מא 3 2 erg pro arg CK CK TAT gln esp tyr בכו חול אל pro phe ser הכא ההם הים פני איני הים אַדָּר פוּדָי אַנָּר AC 550 534 B क्ट उद्ध स्त रिड एक्ट ब्रोव פונם אמר אלם 23 56 20 22 25 3 11 2 · 1082/1398 8551/2851. 8291/2761 1791/1108 7931/2611 8101/1701 1172/1618 7921/2641 8371/2791 8461/2821 1162/1678 821/2941 1762/2169 ğ VAL

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| 3 | 75 0 | 5 7 | | ٢ يو | 15 25 | 2 | Pi. | 1 | als ser | | ≨. გ. | 2 | į | | | E | 130 | į | 2 | | er E | let iser | Ī | | 3 | Ž. | ř. | 1 | 3 2 | |
| ייא גיד איר איר | | 5 | | | | ţ | .pra | ź | 7 | | 8. | 8 F | Ę | : | | R | 623 | B | 1 | | E | | K | ት የ | 3 | 7. | દુ | | li E | |
| | ž | F å | | | 3 | | 5 | 3 | รู | | | ξ. | H | | , | | 715 | Ė | | | | 2 | į | Ä | Ž | 3 | 8 | Cly Cly | 7.5 | |
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| | | ב ב | | fi d | Y | Ë. | į | 1 | 2 | į | វ | o de | 3 | इस संद | | 5 | 5 | X | 65 | | ទី: | 2 | 3 | gle | 3 | ŗ | 3 | | 35 | |
| # * | | ti g | | 3 | | ð. | <u> </u> | . g | 62 | | ֓֞֝֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓ | D : . | , 8 | G | -4 | ţ | <u>.</u> | 3 | J. | | <u>ş</u> . | :i | Ē | | ์ ฮ์ | | : 5 | | E : | |
| Figure 1H | 2 S | g : | /306 | 3 | 7309 | į. |] e | 1 | 2 | 215 | 3 | קא. היי | , , | 2 | 1321. | 5 | 27.5 | F | 2 | רנני | F: | 2000 | × | , usi | F | he i | ti | 23 | 8 1 | |
| Figure | 11e 1ys as:: 5091/3031 | כאס הכא זכד מזכ פוח בכב פבריעפן | 9181/3061 | 3 : : : : : : : : : : : : : : : : : : : | 9271/3091. | والد المادية | ייין זיין ואר מזניוויואנט | TIC 115 CO. | leu ieu pro leu leu | 9451/3151 | 15 15 15 15 15 15 15 15 15 15 15 15 15 1 | ottivial | 155 11 TO | : 5 le C3 | 9631/3211 | באנ אזר אבד מנא | 510 asm ser 9721/3241 | 3 | ser leu alu ash val | 9811/117 | 35 ti. | 659 leu Çir. Nis leu 9501/3301 | שני היה ניש | gly asn val | בנא זה יבי אנא אבא | val phe arg | אבא איא איא דיא איני | CCK pro 11e 10171/3391 | 25 CC TC CC 25 CC 25 ET 3 E C 25 ET 3 ET 3 E C 25 ET 3 ET 3 E C 25 ET 3 ET | |
| | | _ 0 | | . | | J | , 0 | . 64 | -1 | יים | נ ט | . 0 | n þ | | Q | 17 | UP | . [| • | 9 | G | 4 0 | G | ני מ | , 6 | > - | 1 1 | 0 = | 7 d | |

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设计

לכם בעו כבא פטא אוב אכד פלם ככון ביצי באבי כלבי មី រ៉ BB ă i ម ¥ i z g 10291/3431 TEA GAS TOC ACE ATA TOC COT OTO AM TAC OPA glu cys the ile cys sif wal lys tye CCC 755 GCG C GAC CIT 8.5 tz i is a סבד ככב אאם מככ יש! בוץ ואש בוץ K ii Ed 10381/3461 ACT GIT GGS 7 Chr val cly 3 10471/3491 10261/3421

Figure 11

WO 02/061105 PCT/EP02/01633

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DNA sequence 10511 b.p. AAGCTTTACTCG - ACGGCCAGTGCC linear aag oft tac tog taa ago gag tig aag gat cat att tag tig ogt tia Lys Leu Tyr Ser OCH Ser Glu Leu Lys Asp His Ile AMB Leu Arg Leu tga gat aag att gaa agc acg tgt aaa atg ttt ccc gcg cgt tgg cac OPA Asp Lys Ile Glu Ser Thr Cys Lys Met Phe Pro Ala Arg Trp His aac tat tta caa tgc ggc caa gtt ata aaa gat tct aat ctg ata tgt Asn Tyr Leu Gln Cys Gly Gln Val Ile Lys Asp Ser Asn Leu Ile Cys ttt aaa aca cct ttg cgg ccc gag ttg ttt gcg tac gtg act agc gaa 192 Phe Lys Thr Pro Leu Arg Pro Glu Leu Phe Ala Tyr Val Thr Ser Glu gaa gat gtg tgg acc gca gaa cag ata gta aaa caa aac cct agt att Glu Asp Val Trp Thr Ala Glu Gln Ile Val Lys Gln Asn Pro Ser Ile 70 gga gca ata atc gat tta acc aac acg tct aaa tat tat gat ggt gtg 288 Gly Ala Ile Ile Asp Leu Thr Asn Thr Ser Lys Tyr Tyr Asp Gly Val 85 cat ttt ttg cgg gcg ggc ctg tta tac aaa aaa att caa gta cct ggc His Phe Leu Arg Ala Gly Leu Leu Tyr Lys Lys Ile Gln Val Pro Gly 100 105 cag act ttg ccg cct gaa agc ata gtt caa gaa ttt att gac acg gta Gln Thr Leu Pro Pro Glu Ser Ile Val Gln Glu Phe Ile Asp Thr Val 115 120 aaa gaa ttt aca gaa aag tgt ccc ggc atg ttg gtg ggc gtg cac tgc 432 Lys Glu Phe Thr Glu Lys Cys Pro Gly Met Leu Val Gly Val His Cys 130 135 aca cac ggt att aat cgc acc ggt tac atg gtg tgc aga tat tta atg 480 Thr His Gly Ile Asn Arg Thr Gly Tyr Met Val Cys Arg Tyr Leu Met 145 150 cac acc ctg ggt att gcg ccg cag gaa gcc ata gat aga ttc gaa aaa His Thr Leu Gly Ile Ala Pro Gln Glu Ala Ile Asp Arg Phe Glu Lys 165 gcc aga ggt cac aaa att gaa aga caa aat tac gtt caa gat tta tta 576 Ala Arg Gly His Lys Ile Glu Arg Gln Asn Tyr Val Gln Asp Leu Leu 180 att taa tta ata tta ttt gca ttc ttt aac aaa tac ttt atc cta ttt 624 Ile OCH Leu Ile Leu Phe Ala Phe Phe Asn Lys Tyr Phe Ile Leu Phe 195 tca aat tgt tgc gct tct tcc agc gaa cca aaa cta tgc ttc gct tgc 672 Ser Asn Cys Cys Ala Ser Ser Ser Glu Pro Lys Leu Cys Phe Ala Cys 210

Figure 2A

| tcc Ser 225 | gtt Val | tag AMB | ctt Leu | gta Val | gcc Ala 230 | gat Asp | cag Gln | tgg Trp | cgt Arg | tgt Cys 235 | tcc Ser | aat Asn | cga Arg | cgg Arg | tag AMB 240 | 720 |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------|
| gat Asp | tag AMB | gcc Ala | gga Gly | tat Tyr 245 | tct Ser | cca Pro | cca Pro | caa Gln | tgt Cys 250 | tgg Trp | caa Gln | cgt Arg | tga OPA | tgt Cys 255 | tac Tyr | 768 |
| gtt Val | tat Tyr | gct Ala | ttt Phe 260 | ggt Gly | ttt Phe | cca Pro | cgt Arg | acg Thr 265 | tct Ser | ttt Phe | Gly | cgg Arg | taa OCH 270 | tag AMB | ccg Pro | 816 |
| taa OCH | acg Thr | tag AMB 275 | tgc Cys | cgt Arg | cgc Arg | gcg Ala | tca Ser 280 | egc Arg | aca Thr | aca Thr | ccg Pro | gat Asp 285 | gtt Val | tgc Cys | gct Ala | 864 |
| tgt Cys | ccg Pro 290 | cgg Arg | ggt Gly | att Ile | gaa Glu | ccg Pro 295 | cgc Arg | gat Asp | ccg Pro | aca Thr | aat Asn 300 | cca Pro | cca Pro | ctt Leu | tgg Trp | 912 |
| caa Gln 305 | cta Leu | aat Asn | cgg Arg | tga OPA | cct Pro 310 | gcg Ala | cgt Arg | ctt Leu | ttt Phe | tct Ser 315 | gca Ala | tta Leu | ttt Phe | cgt Arg | ctt Leu 320 | 960 |
| tct Ser | ttt Phe | gca Ala | tgg Trp | ttt Phe 325 | cct Pro | gga Gly | agc Ser | cgg Arg | tgt Cys 330 | aca Thr | tgc Cys | ggt Gly | tta Leu | gat Asp 335 | cag Gln | 1008 |
| tca Ser | tga OPA | cgc Arg | gcg Ala 340 | tga OPA | cct Pro | gca Ala | aat' Asn | ctt Leu 345 | tgg Trp | cct Pro | cga | tct Ser | gct Ala 350 | tgt Cys | cct Pro | 1056 |
| | | | | | | | taa OCH 360 | | | | | | | | | 1104 |
| | | | | | | _ | ctt Leu | | _ | | _ | _ | | | | 1152 |
| _ | _ | | | _ | - | | cca Pro | | | | | | | | _ | 1200 |
| _ | _ | _ | | _ | _ | | tgc Cys | | _ | _ | _ | | | _ | | 1248 |
| | | | | | | | gta Val | | | | | | | | | 1296 |
| | | | Ser | | | | cgc Arg 440 | | | | | | | | | 1344 |
| gcg Ala | gct Ala 450 | Ala | aat Asn | aca Thr | gcg Ala | ggt Gly 455 | cgc | ccc Pro | ttt Phe | tca Ser | cga Arg 460 | cgc Arg | tgt Cys | tag AMB | agg Arg | 1392 |

Figure 2B

WO 02/061105

| tag AMB 465 | ggc Gly | ccc Pro | cat His | ttt Phe | gga Gly 470 | tgg Trp | tct Ser | gct Ala | caa Gln | ata Ile 475 | acg Thr | att Ile | tgt Cys | att Ile | tat Tyr 480 | 1440 |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|---------------------|-------------------|-------------------|-------------------|-------------------|---------------------|-------------------|-----------|
| tgt Cys | cta Leu | cat His | gaa Glu | cac His 485 | gta Val | tag AMB | ctt | tat Seu 7 | cac Cyr I 490 | aaa His I | ctg Lys 1 | tat Leu 1 | att Tyr : | tta Ile I 495 | aac Jeu As | 1488 n |
| tgt Cys | tag AMB | cga Arg | cgt Arg 500 | cct Pro | tgg Trp | cca Pro | cga Arg | acc Thr 505 | gga Gly | cct Pro | gtt Val | ggt Gly | cgc Arg 510 | gct Ala | cta Leu | 1536 |
| gca Ala | cgt Arg | acc Thr 515 | gca Ala | ggt Gly | tga OPA | acg Thr | tat Tyr 520 | ctt Leu | ctc Leu | caa Gln | att Ile | taa OCH 525 | att Ile | ctc Leu | caa Gln | 1584 |
| ttt Phe | taa OCH 530 | cgc Arg | gag Glu | cca Pro | ttt Phe | tga OPA 535 | tac Tyr | acg Thr | tgt Cys | gtc Val | gat Asp 540 | ttt Phe | gca Ala | aca Thr | act Thr | 1632 |
| att Ile 545 | gtt Val | ttt Phe | taa OCH | cgc Arg | aaa Lys 550 | cta Leu | aac Asn | tta Leu | ttg Leu | tgg Trp 555 | taa OCH | gca Ala | ata Ile | att Ile | aaa Lys 560 | 1680 |
| tat Tyr | 999 Gly | gga Gly | aca Thr | tgc Cys 565 | gcc Ala | gct Ala | aca Thr | aca Thr | ctc Leu 570 | gtc Val | gtt Val | atg Met | aac Asn | gca Ala 575 | gac Asp | 1728 |
| ggc Gly | gcc Ala | ggt Gly | ctc Leu 580 | ggc | gca Ala | agc Ser | ggc | taa OCH 585 | aac Asn | gtg Val | ttg Leu | cgc Arg | gtt Val 590 | caa Gln | cgc Arg | 1776 |
| ggc | aaa Lys | cat His 595 | cgc Arg | aaa Lys | agc Ser | caa Gln | tag AMB 600 | tac Tyr | agt Ser | ttt Phe | gat Asp | ttg Leu 605 | cat His | att Ile | aac Asn | 1824 |
| ggc | gat Asp 610 | Phe | tta Leu | aat Asn | tat Tyr | ctt Leu 615 | att Ile | taa OCH | taa OCH | ata Ile | gtt Val 620 | atg Met | acg Thr | cct Pro | aca Thr | 1872 |
| | | | | | | | | | | | | | | tga OPA | | 1920 |
| | | | | | | | | | | | | | | cca Pro 655 | | 1968 |
| | | | | | | | | | | | | | | cgt Arg | | 2016 |
| | | | Arg | | | | | | | | | | | gaa Glu | | 2064 |
| | | Ser | | | | | | | | | | | | gca Aļa | | 2112 |

Figure 2C

| acg | tcc | gaa | cgt | tga OPA | ttt Dhe | gca Ala | tgc Cvs | aag Lvs | ccg Pro | aaa Lys | tta Leu | aat Asn | cat His | tgc Cys | gat Asp | 2160 |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------|
| 705 | | | | | 710 | | | | | 715 | | | | | 720 | |
| tag AMB | tgc Cys | gat Asp | taa OCH | aac Asn 725 | gtt Val | gta Val | cat His | cct Pro | cgc Arg 730 | ttt Phe | taa OCH | tca Ser | tgc Cys | cgt Arg 735 | cga Arg | 2208 |
| tta Leu | aat Asn | cgc Arg | gca Ala 740 | atc Ile | gag Glu | tca Ser | agt Ser | gat Asp 745 | caa Gln | agt Ser | gtg Val | gaa Glu | taa OCH 750 | tgt Cys | ttt Phe | 2256 |
| ctt Leu | tgt Cys | att Ile 755 | ccc Pro | gag Glu | tca Ser | agc Ser | gca Ala 760 | gcg Ala | cgt Arg | att Ile | tta Leu | aca Thr 765 | aac Asn | tag AMB | cca Pro | 2304 |
| tct Ser | tgt Cys 770 | aag Lys | tta Leu | gtt Val | tca Ser | ttt Phe 775 | aat Asn | gca Ala | act Thr | tta Leu | tcc Ser 780 | aat Asn | aat Asn | ata Ile | tta Leu | 2352 |
| tgt Cys 785 | atc Ile | gca Ala | cgt Arg | caa Gln | gaa Glu 790 | tta Leu | aca Thr | atg Met | cgc Arg | ccg Pro 795 | ttg Leu | tcg Ser | cat His | ctc Leu | aac Asn 800 | 2400 |
| acg Thr | act Thr | atg Met | ata Ile | gag Glu 805 | atc Ile | aaa Lys | taa OCH | agc Ser | gcg Ala 810 | aat Asn | taa OCH | ata Ile | gct Ala | tgc Cys 815 | gac Asp | 2448 |
| gca Ala | acg Thr | tgc Cys | acg Thr 820 | atc Ile | tgt Cys | gca Ala | Arg Cgc | gtt Val 825 | ccg Pro | gca Ala | cga Arg | gct Ala | ttg Leu 830 | att Ile | gta Val | 2496 |
| ata Ile | agt Ser | ttt Phe 835 | tac Tyr | gaa Glu | gcg Ala | atg Met | aca Thr 840 | tga OPA | ccc Pro | ccg Pro | tag AMB | tga OPA 845 | caa Gln | cga Arg | tca Ser | 2544 |
| cgc Arg | cca Pro 850 | aaa Lys | gaa Glu | ctg Leu | ccg Pro | act Thr 855 | aca Thr | aaa Lys | tta Leu | ccg Pro | agt Ser 860 | atg Met | tcg Ser | gtg Val | acg Thr | 2592 |
| | Lys | | | agc Ser | | | | | | | | | | | | 2640 |
| | | | | ccg Pro 885 | | | | | | | | | | | | 2688 |
| | | | | aga Arg | | | | | | | | | | | | 2736 |
| | | | Asp | gat Asp | | | | Lys | | | | | | | | 2784 |
| | | Tyr | | ggc Gly | | | Leu | | | | | | | | | 2832 |

Figure 2D

| tac atg ctg tta Tyr Met Leu Leu 945 | a acg gct ccg 1 Thr Ala Pro 950 | ccc act att Pro Thr Ile | aat gaa att a Asn Glu Ile I 955 | ys Asn Ser 960 | 880 |
|---|--|--|---|---------------------------------------|-----|
| aat ttt aaa aaa Asn Phe Lys Ly | a cgc agc aag s Arg Ser Lys 965 | aga aac att Arg Asn Ile 970 | Cys Met Lys | gaa tgc gta 29 Slu Cys Val 975 | 928 |
| gaa gga aag aa Glu Gly Lys Lys 98 | s Asn Val Val | gac atg ctg Asp Met Leu 985 | Asn Asn Lys | itt aat atg 29 Net Asn Met 1990 | 976 |
| cct ccg tgt at Pro Pro Cys Il 995 | a aaa aaa ata e Lys Lys Ile | ttg aac gat Leu Asn Asp 1000 | ttg aaa gaa a Leu Lys Glu 1 1005 | ac aat gta 30 Asn Asn Val | 024 |
| ccg cgc ggc gg Pro Arg Gly Gl | t atg tac agg y Met Tyr Arg 1015 | Lys Arg Phe | ata cta aac 1 Ile Leu Asn (1020 | gt tac att 30 Cys Tyr Ile | 072 |
| gca aac gtg gt Ala Asn Val Va 1025 | t tcg tgt gcc l Ser Cys Ala 1030 | aag tgt gaa Lys Cys Glu | aac cga tgt 1 .Asn Arg Cys 1 1035 | tta atc aag 33 Leu Ile Lys 1040 | 120 |
| gct ctg acg ca Ala Leu Thr Hi | t ttc tac aac s Phe Tyr Asn 1045 | cac gac tcc His Asp Ser 1050 | Lys Cys Val (| ggt gaa gtc 3 Gly Glu Val 1055 | 168 |
| atg cat ctt tt Met His Leu Le 106 | u Ile Lys Ser | caa'gat gtg Gln Asp Val | Tyr Lys Pro | cca aac tgc 33 Pro Asn Cys 070 | 216 |
| caa aaa atg aa Gln Lys Met Ly 1075 | a act gtc gac s Thr Val Asp | : aag ctc tgt > Lys Leu Cys 1080 | ccg ttt gct (Pro Phe Ala (| ggc aac tgc 3 Gly Asn Cys | 264 |
| aag ggt ctc aa Lys Gly Leu As 1090 | t cct att tgt n Pro Ile Cys 1095 | Asn Tyr OPA | ata ata aaa A Ile Ile Lys (1100 | caa tta taa 3 Gln Leu OCH | 312 |
| atg cta aat tt Met Leu Asn Le 1105 | g ttt ttt att u Phe Phe Ile 1110 | aac gat aca Asn Asp Thi | aac caa acg Asn Gln Thr | caa caa gaa 3 Gln Gln Glu 1120 | 360 |
| cat ttg tag ta His Leu AMB Ty | t tat cta tag r Tyr Leu OCF 1125 | a ttg aaa acg H Leu Lys Thi 1130 | Arg Ser Tyr . | aat cgc tga 3 Asn Arg OPA 1135 | 408 |
| ggt aat att ta Gly Asn Ile OO 114 | H Asn His Phe | | His Ser OCH | | 456 |
| ata taa ttt ta Ile OCH Phe Ty 1155 | | | | | 504 |
| cgt att cct to Arg Ile Pro Se 1170 | | s Phe Ser Pro | | | 552 |

Figure 2E

| tat tat cgt atc cat ata Tyr Tyr Arg Ile His Ile 1185 1190 | Cys Ile Tyr Arg | ata gag taa att ttt tgt Ile Glu OCH Ile Phe Cys 195 1200 | 3600 |
|---|--|--|------|
| tgt cat aaa tat ata tgt Cys His Lys Tyr Ile Cys 1205 | ctt ttt taa tgg Leu Phe OCH Trp 1210 | ggt gta tag tac ege tge Gly Val AMB Tyr Arg Cys 1215 | 3648 |
| gca tag ttt ttc tgt aat Ala AMB Phe Phe Cys Asn 1220 | tta caa cag tgc Leu Gln Gln Cys 1225 | tat ttt ctg gta gtt ctt Tyr Phe Leu Val Val Leu 1230 | 3696 |
| cgg agt gtg ttg ctt taa Arg Ser Val Leu Leu OCH 1235 | tta tta aat tta Leu Leu Asn Leu 1240 | tat aat caa tga att tgg Tyr Asn Gln OPA Ile Trp 1245 | 3744 |
| Asp Arg Arg Phe Cys Thr | ata tgt tgc cgg Ile Cys Cys Arg 1255 | cat agt acg cag ctt ctt His Ser Thr Gln Leu Leu 1260 | 3792 |
| | Phe Leu Ala Ala | ccg gat taa cat aac ttt Pro Asp OCH His Asn Phe 275 1280 | 3840 |
| | | aca gtt cac ctc cct ttt Thr Val His Leu Pro Phe 1295 | 3888 |
| | | tgt taa aaa taa cag cca Cys OCH Lys OCH Gln Pro 1310 | 3936 |
| | | aac tgg aaa tgt cta tca Asn Trp Lys Cys Leu Ser 1325 | 3984 |
| Ile Tyr Ser Cys OPA Tyr | | taa aat gat aac cat ctc OCH Asn Asp Asn His Leu 1340 | 4032 |
| | Tyr Cys Phe Arg | aac agt ttt gta ata aaa Asn Ser Phe Val Ile Lys 355 1360 | 4080 |
| | | cgt ccc acc atc ggg cgc Arg Pro Thr Ile Gly Arg 1375 | 4128 |
| gga tct atg cta cta gta Gly Ser Met Leu Leu Val 1380 | aat cag tca cac Asn Gln Ser His 1385 | caa ggc ttc aat aag gaa Gln Gly Phe Asn Lys Glu 1390 | 4176 |
| His Thr Ser Lys Met Val 1395 | Ser Ala Ile Val 1400 | Leu Tyr Val Leu Leu Ala 1405 | 4224 |
| Ala Ala Ala His Ser Ala | ttt gcg gcg gat Phe Ala Ala Asp 1415 | ctt gga tcc cat cat cac Leu Gly Ser His His His 1420 | 4272 |

Figure 2F

| cac cac cac att gaa gga aga gaa ttc cag gtc caa ctg cag cag tct His His His Ile Glu Gly Arg Glu Phe Gln Val Gln Leu Gln Gln Ser 1425 1430 1435 1440 | 4320 |
|---|------|
| ggg gct gaa ctg gca aaa cct ggg gcc tca gtg aag ctg tcc tgc aag Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val Lys Leu Ser Cys Lys 1445 1450 1455 | 4368 |
| gct tct ggc cac acc ttt act agc tac tgg atg cac tgg gta aaa cag Ala Ser Gly His Thr Phe Thr Ser Tyr Trp Met His Trp Val Lys Gln 1460 1465 1470 | 4416 |
| agg cct gga cag ggt ctg gaa tgg att gga tac att aat ctt agc agt Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Leu Ser Ser 1475 1480 1485 | 4464 |
| ggt tat att aag tac aat cag gag ttc aag gac aag gcc aca ttg act Gly Tyr Ile Lys Tyr Asn Gln Glu Phe Lys Asp Lys Ala Thr Leu Thr 1490 1495 1500 | 4512 |
| gca gac aaa tcc tcc aac aca gcc tac atg cat ctg agc agc ctg aca Ala Asp Lys Ser Ser Asn Thr Ala Tyr Met His Leu Ser Ser Leu Thr 1505 1510 1515 1520 | 4560 |
| tat gag gac tot goa gto tat tac tgt goa agg goa got cag got acg Tyr Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ala Ala Gln Ala Thr 1525 1530 1535 | 4608 |
| acc ttt gac tac tgg ggc caa ggc acc act ctc aca gtc tcc tca ggt Thr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly 1540 1545 1550 | 4656 |
| gga ggc ggt tca ggc gga ggt ggc tct ggc ggt ggc gga tcg gac att Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile 1555 1560 1565 | 4704 |
| gtg atg atc cag tct cac aaa ttc atg tcc aca tca gta gga gac agg Val Met Ile Gln Ser His Lys Phe Met Ser Thr Ser Val Gly Asp Arg 1570 1580 | 4752 |
| gtc agc atc acc tgc aag gcc agt cag gat gtg agt act gct gta ggc Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala Val Gly 1585 1590 1595 1600 | 4800 |
| tgg tat caa caa aaa cca ggg caa tct cct aaa cta ctg att tac tgg Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp 1605 1610 1615 | 4848 |
| gca tcc acc cgg cac act gga gtc cct gat cgc ttc aca ggc agt gga Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly 1620 1625 1630 | 4896 |
| tct ggg aca gat tat act ctc acc atc agc agt gtg cag gct gaa gac Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp 1635 1640 1645 | 4944 |
| ctg gca ctt tat tac tgt cag caa cat tat agc act cct ccg acg ttc Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Pro Thr Phe 1650 1660 | 4992 |

Figure 2G

| ggt gga ggc acc Gly Gly Gly Thr 1665 | aag ctg gga a Lys Leu Gly 1 | Ile Lys Arg | gct ccc ggg g Ala Pro Gly G .675 | ga tgt taa ly Cys OCH 1680 | 5040 |
|--|--|------------------------------|--|----------------------------------|------|
| aga tot gat cot Arg Ser Asp Pro | | | | | 5088 |
| ttc aag gaa atc Phe Lys Glu Ile 1700 | Arg Asn Val I | | | eu Val Val | 5136 |
| gga tgg aaa gga Gly Trp Lys Gly 1715 | Lys Glu Phe T | | | | 5184 |
| gaa gac agc ttc Glu Asp Ser Phe 1730 | _ | _ | | _ | 5232 |
| ctt gtt gtc aac Leu Val Val Asn 1745 | | hr Arg Pro | | | 5280 |
| ctg gcc caa cac Leu Ala Gln His | | | | | 5328 |
| gtg att agg atc Val Ile Arg Ile 1780 | gtc gag cct t Val Glu Pro S | ca'tgg gtg er Trp Val | ggc agc aac aa Gly Ser Asn As 179 | sn Glu Tyr | 5376 |
| cgc atc agc ctg Arg Ile Ser Leu 1795 | Ala Lys Lys G | gc ggc ggc (| tgc cca ata at Cys Pro Ile Me 1805 | g aac ctt et Asn Leu | 5424 |
| cac tct gag tac His Ser Glu Tyr 1810 | acc aac tcg t Thr Asn Ser P 1815 | tc gaa cag : he Glu Gln : | ttc atc gat co Phe Ile Asp Ar 1820 | t gtc atc g Val Ile | 5472 |
| tgg gag aac ttc Trp Glu Asn Phe 1825 | Tyr Lys Pro I 1830 | le Val Tyr : | Ile Gly Thr As 335 | p Ser Ala 1840 | 5520 |
| | Ile Leu Leu G 1845 | lu Val Ser 1 1850 | Leu Val Phe Ly | s Val Lys 1855 | 5568 |
| gag ttt gca cca Glu Phe Ala Pro 1860 | Asp Ala Pro L | eu Phe Thr (1865 | Gly Pro Ala Ty 187 | r OCH Asn 0 | 5616 |
| acg ata cat tgt Thr Ile His Cys 1875 | Tyr AMB Tyr I 18 | le Tyr OCH # 80 | lla Leu Asp Se 1885 | r Val Arg | 5664 |
| tgt tga ttt aca Cys OPA Phe Thr 1890 | gac aat tgt t Asp Asn Cys C 1895 | gt acg tat t ys Thr Tyr I | tt aat aat tc he Asn Asn Se 1900 | a tta aat r Leu Asn | 5712 |

Figure 2H

| tta taa tot tta ggg Leu OCH Ser Leu Gly 1905 | | | s Ile Lys OPA | |
|--|------------------------------------|------------------------------------|--|-------------------------|
| gcg tct tta tat ctg Ala Ser Leu Tyr Leu 1925 | | | r Ser Ile Asp | |
| aat agg ttt cga tta Asn Arg Phe Arg Leu 1940 | | | | |
| gct gga cta tct aat Ala Gly Leu Ser Asn 1955 | | Leu Asn Ala | | |
| tct tgt agc agc aat Ser Cys Ser Ser Asn 1970 | | | | |
| tgt aat aaa ggt tcg Cys Asn Lys Gly Ser 1985 | | | Cys Ala Phe | _ |
| ctt tca tca ctg tcg Leu Ser Ser Leu Ser 2005 | | _ | Asp Val Asn | _ |
| aat aaa gct tgg aca Asn Lys Ala Trp Thr 2020 | Tyr Leu Thr | tcg ggc gtg Ser Gly Val 2025 | tta gct tta Leu Ala Leu 2030 | tta ggc 6096 Leu Gly |
| cga tta tcg tcg tcg Arg Leu Ser Ser Ser 2035 | tcc caa ccc Ser Gln Pro 2040 | tcg tcg tta Ser Ser Leu | gaa gtt gct Glu Val Ala 2045 | tcc gaa 6144 Ser Glu |
| gac gat ttt gcc ata Asp Asp Phe Ala Ile 2050 | gcc aca cga Ala Thr Arg 2055 | Arg Leu Leu | att gtg tcg Ile Val Ser 2060 | gct aac 6192 Ala Asn |
| | Phe Val Val 2070 | Glu Leu Phe 2075 | Gly Ile Ile | Ser Asp 2080 |
| tgc ggg cgt ttt tgg Cys Gly Arg Phe Trp 2085 | Ala Gly Phe | Asn Leu Thr 2090 | Val Pro Asp 2 | Phe Asn 095 |
| tca gac aac acg tta Ser Asp Asn Thr Leu 2100 | Glu Ser Asp | Gly Ala Gly 2105 | Gly Gly Asn 2110 | Ile Ser |
| gac ggc aaa tct act Asp Gly Lys Ser Thr 2115 | Asn Gly Gly 2120 | Gly Gly Gly | Ala Asp Asp 3 | Lys Ser |
| acc atc ggt gga ggc Thr Ile Gly Gly Gly 2130 | gca ggc ggg Ala Gly Gly 2135 | Ala Gly Gly | gga ggc gga g Gly Gly Gly (2140 | ggc gga 6432 Gly Gly |

Figure 21

| ggt ggt ggc ggt gat gca Gly Gly Gly Gly Asp Ala 2145 2150 | Asp Gly Gly Leu Gly | tca aat gtc tct tta 6480 Ser Asn Val Ser Leu 2160 |
|---|--|---|
| ggc aac aca gtc ggc acc Gly Asn Thr Val Gly Thr 2165 | tca act att gta ctg Ser Thr Ile Val Leu 2170 | gtt tcg ggc gcc gtt 6528 Val Ser Gly Ala Val 2175 |
| ttt ggt ttg acc ggt ctg Phe Gly Leu Thr Gly Leu 2180 | aga cga gtg cga ttt Arg Arg Val Arg Phe 2185 | ttt tcg ttt cta ata 6576 Phe Ser Phe Leu Ile 2190 |
| gct tcc aac aat tgt tgt Ala Ser Asn Asn Cys Cys 2195 | ctg tcg tct aaa ggt Leu Ser Ser Lys Gly 2200 | gca gcg ggt tga ggt 6624 Ala Ala Gly OPA Gly 2205 |
| tcc gtc ggc att ggt gga Ser Val Gly Ile Gly Gly 2210 | Ala Gly Gly Asn Ser | |
| ggt ggt ggt gga ggc gct Gly Gly Gly Gly Ala 2225 2230 | gga atg tta ggc acg Gly Met Leu Gly Thr 2235 | gga gaa ggt ggt ggc 6720 Gly Glu Gly Gly Gly 2240 |
| ggc ggt gcc gcc ggt ata Gly Gly Ala Ala Gly Ile 2245 | | |
| att gtg ggc acc ggc gca Ile Val Gly Thr Gly Ala 2260 | | |
| ctg ctt cga ggc agc gct Leu Leu Arg Gly Ser Ala 2275 | | |
| gaa tac aaa tcg taa aaa Glu Tyr Lys Ser OCH Lys 2290 | Ser Ala Ile Ser Ile | |
| ttt acc gtg ccg ata ttt Phe Thr Val Pro Ile Phe 2305 2310 | | |
| taa aga gat tgt ctc aag OCH Arg Asp Cys Leu Lys 2325 | ctc cgc acg ccg ata Leu Arg Thr Pro Ile 2330 | aca agc ctt ttc att 7008 Thr Ser Leu Phe Ile 2335 |
| Phe Thr Thr Ala Leu AMB 2340 | tgg cga gac act tcg Trp Arg Asp Thr Ser 2345 | ctg tcg tcg acg tac 7056 Leu Ser Ser Thr Tyr 2350 |
| atg tat gct ttg ttg tca Met Tyr Ala Leu Leu Ser 2355 | aaa acg tcg ttg gca Lys Thr Ser Leu Ala 2360 | agc ttt aaa ata ttt 7104 Ser Phe Lys Ile Phe 2365 |
| aaa aga aca tct ctg ttc Lys Arg Thr Ser Leu Phe 2370 | Ser Thr Thr Val Leu | tcg taa atg ttg ttt 7152 Ser OCH Met Leu Phe 380 |

Figure 2J

| ttg ata att tgc Leu Ile Ile Cys 2385 | gct tcc gca g Ala Ser Ala V 2390 | ta tcg aca cgt al Ser Thr Arg 2395 | tca aaa aat tga tgc Ser Lys Asn OPA Cys 2400 | 7200 |
|--|--|--|--|------|
| Ala Ser Ile Leu | ttg ttc cta t Leu Phe Leu L 2405 | ta ttg aat aaa eu Leu Asn Lys 2410 | taa gat tgt aca gat OCH Asp Cys Thr Asp 2415 | 7248 |
| tca tat cta cga Ser Tyr Leu Arg 2420 | ttc gtc atg g Phe Val Met A | cc acc aca aat la Thr Thr Asn 2425 | gct acg ctg caa acg Ala Thr Leu Gln Thr 2430 | 7296 |
| ctg gta caa ttt Leu Val Gln Phe 2435 | tac gaa aac t Tyr Glu Asn C | ys Lys Asn Val | aaa act cgg tat aaa Lys Thr Arg Tyr Lys 2445 | 7344 |
| | | ys Ile Ser Ile : | tta tcg cac aag ccc Leu Ser His Lys Pro 460 | 7392 |
| | | | gcg cac aat ttt aac Ala His Asn Phe Asn 2480 | 7440 |
| Ala Asp Glu Ile | | | gac cac cca aat ttt Asp His Pro Asn Phe 2495 | 7488 |
| | | | aac caa gtg atc gtg Asn Gln Val Ile Val 2510 | 7536 |
| | | sp Leu Phe Glu ' | aca cta caa att aaa Thr Leu Gln Ile Lys 2525 | 7584 |
| | | al Ser Asn Ile : | att aga cag ctg tgt Ile Arg Gln Leu Cys 540 | 7632 |
| | | | ata cac aac gac ata Ile His Asn Asp Ile 2560 | 7680 |
| Lys Leu Glu Asn | gtc tta tat to Val Leu Tyr Pl 2565 | to gaa goa ott q ne Glu Ala Leu) 2570 | gat ege gtg tat gtt Asp Arg Val Tyr Val 2575 | 7728 |
| tgc gat tac gga Cys Asp Tyr Gly 2580 | ttg tgc aaa ca Leu Cys Lys H | ac gaa aac tca d is Glu Asn Ser 1 2585 | ctt agc gtg cac gac Leu Ser Val His Asp 2590 | 7776 |
| ggc acg ttg gag Gly Thr Leu Glu 2595 | tat ttt agt co Tyr Phe Ser Pr 260 | ro Glu Lys Ile A | cga cac aca act atg Arg His Thr Thr Met 2605 | 7824 |
| cac gtt tcg ttt His Val Ser Phe | gac tgg tac g | eg geg tgt taa d | cat aca agt tgc taa | 7872 |

Figure 2K

| ccg gcg gtt cgt aat cat gg Pro Ala Val Arg Asn His Gl 2625 2630 | t cat agc tgt ttc ctg tgt gaa att gtt 79 y His Ser Cys Phe Leu Cys Glu Ile Val 2635 2640 | 920 |
|---|---|-----|
| | a aca tac gag ccg gaa gca taa agt gta 79 r Thr Tyr Glu Pro Glu Ala OCH Ser Val 2650 2655 | 968 |
| aag cct ggg gtg cct aat gag Lys Pro Gly Val Pro Asn Gly 2660 | g tga gct aac tca cat taa ttg cgt tgc 80 u OPA Ala Asn Ser His OCH Leu Arg Cys 2665 2670 | 016 |
| | t cgg gaa acc tgt cgt gcc agc tgc att 80 r Arg Glu Thr Cys Arg Ala Ser Cys Ile 2680 2685 | 064 |
| | Gly Glu Ala Val Cys Val Leu Gly Ala | 112 |
| | g act cgc tgc gct cgg tcg ttc ggc tgc 81 u Thr Arg Cys Ala Arg Ser Phe Gly Cys 2715 2720 | 60 |
| | t caa agg cgg taa tac ggt tat cca cag 82 r Gln Arg Arg OCH Tyr Gly Tyr Pro Gln 2730 2735 | :08 |
| | a aga aca tgt gag caa aag gcc agc aaa 82 1 Arg Thr Cys Glu Gln Lys Ala Ser Lys 2745 2750 | :56 |
| | g ccg cgt tgc tgg cgt ttt tcc ata ggc 83 g Pro Arg Cys Trp Arg Phe Ser Ile Gly 2760 2765 | 04 |
| tec gee eee etg acg age atc Ser Ala Pro Leu Thr Ser Ile 2770 2775 | Thr Lys Ile Asp Ala Gln Val Arg Gly | 52 |
| | t aaa gat acc agg cgt ttc ccc ctg gaa 84 r Lys Asp Thr Arg Arg Phe Pro Leu Glu 2795 2800 | 00 |
| gct ccc tcg tgc gct ctc ctg Ala Pro Ser Cys Ala Leu Leu 2805 | ttc cga ccc tgc cgc tta ccg gat acc 840 Phe Arg Pro Cys Arg Leu Pro Asp Thr 2810 2815 | 48 |
| tgt ccg cct ttc tcc ctt cgg Cys Pro Pro Phe Ser Leu Arg 2820 | g gaa gcg tgg cgc ttt ctc ata gct cac 849 g Glu Ala Trp Arg Phe Leu Ile Ala His 2825 2830 | 96 |
| Ala Val Gly Ile Ser Val Arg 2835 | g tgt agg tcg ttc gct cca agc tgg gct 854 g Cys Arg Ser Phe Ala Pro Ser Trp Ala 2840 2845 | 44 |
| gtg tgc acg aac ccc ccg ttc Val Cys Thr Asn Pro Pro Phe 2850 . 2855 | e age deg ade get geg det tat deg gta 859 e Ser Pro Thr Ala Ala Pr Tyr Pro Val 2860 | 92 |

Figure 2L

| act atc gtc ttg agt cca Thr Ile Val Leu Ser Pro 2865 2870 | Thr Arg OCH Asp | acg act tat cgc cac tgg 8 Thr Thr Tyr Arg His Trp 2875 2880 | 3640 |
|---|--|--|------|
| cag cag cca ctg gta aca Gln Gln Pro Leu Val Thr 2885 | gga tta gca gag Gly Leu Ala Glu 2890 | cga ggt atg tag gcg gtg 8 Arg Gly Met AMB Ala Val 2895 | 8688 |
| cta cag agt tct tga agt Leu Gln Ser Ser OPA Ser 2900 | ggt ggc cta act Gly Gly Leu Thr 2905 | acg gct aca cta gaa gga 8 Thr Ala Thr Leu Glu Gly 2910 | 3736 |
| cag tat ttg gta tct gcg Gln Tyr Leu Val Ser Ala 2915 | ctc tgc tga agc Leu Cys OPA Ser 2920 | cag tta cct tcg gaa aaa 8 Gln Leu Pro Ser Glu Lys 2925 | 1784 |
| gag ttg gta gct ctt gat Glu Leu Val Ala Leu Asp 2930 | ccg gca aac aaa Pro Ala Asn Lys 2935 | cca ccg ctg gta gcg gtg 8 Pro Pro Leu Val Ala Val 2940 | |
| | Ser Arg Leu Arg | gca gaa aaa aag gat ctc 8 Ala Glu Lys Lys Asp Leu 2955 2960 | 880 |
| | | ctg acg ctc agt gga acg 8 Leu Thr Leu Ser Gly Thr 2975 | 928 |
| | | gat tat caa aaa gga tct 8 Asp Tyr Gln Lys Gly Ser 2990 | 976 |
| | _ | gtt tta aat caa tct aaa 99 Val Leu Asn Gln Ser Lys 3005 | 024 |
| | | acc aat gct taa tca gtg 99 Thr Asn Ala OCH Ser Val 3020 | 072 |
| agg cac cta tct cag cga Arg His Leu Ser Gln Arg 3025 3030 | Ser Val Tyr Phe | gtt cat cca tag ttg cct 99 Val His Pro AMB Leu Pro 3035 3040 | 120 |
| gac tcc ccg tcg tgt aga Asp Ser Pro Ser Cys Arg 3045 | taa cta cga tac OCH Leu Arg Tyr 3050 | ggg agg gct tac cat ctg 93 Gly Arg Ala Tyr His Leu 3055 | 168 |
| Ala Pro Val Leu Gln OPA 3060 | Tyr Arg Glu Thr 3065 | His Ala His Arg Leu Gln 3070 | 216 |
| Ile Tyr Gln Gln OCH Thr 3075 | Ser Gln Pro Glu 3080 | Gly Pro Ser Ala Glu Val 3085 | 264 |
| Val Leu Gln Leu Tyr Pro | cct cca tcc agt Pro Pro Ser Ser 3095 | Cta tta att gtt gcc ggg 93 Leu Leu Ile Val Ala Gly 3100 | 312 |

Figure 2M

| aag cta gag taa gta gt Lys Leu Glu OCH Val Val 3105 3110 | l Arg Gln Leu | ata gtt tgc gca Ile Val Cys Ala 3115 | acg ttg ttg 936 Thr Leu Leu 3120 |
|---|------------------------------------|--|---|
| cca ttg cta cag gca tcg Pro Leu Leu Gln Ala Ser 3125 | Trp Cys His | gct cgt cgt ttg Ala Arg Arg Let 3130 | gta tgg ctt 940 Val Trp Leu 3135 |
| cat tca gct ccg gtt ccc His Ser Ala Pro Val Pro 3140 | aac gat caa Asn Asp Gln 3145 | ggc gag tta cat Gly Glu Leu His | gat ccc cca 945 Asp Pro Pro 3150 |
| tgt tgt gca aaa aag cgg Cys Cys Ala Lys Lys Arg 3155 | tta gct cct Leu Ala Pro 3160 | tcg gtc ctc cga Ser Val Leu Arg 3165 | Ser Leu Ser |
| gaa gta agt tgg ccg cag Glu Val Ser Trp Pro Gli 3170 | | | |
| ata att ctc tta ctg tca Ile Ile Leu Leu Leu Ser 3185 3190 | Cys His Pro | | |
| gtg agt act caa cca agt Val Ser Thr Gln Pro Ser 3205 | His Ser Glu | | |
| gtt gct ctt gcc cgg cgt Val Ala Leu Ala Arg Arg 3220 | | Ile Ile Pro Arg | |
| gaa ctt taa aag tgc tca Glu Leu OCH Lys Cys Ser 3235 | | | |
| tct caa gga tct tac cgc Ser Gln Gly Ser Tyr Arg 3250 | | | |
| gtg cac cca act gat ctt Val His Pro Thr Asp Let 3265 3270 | Gln His Leu | | |
| ggt gag caa aaa cag gaa Gly Glu Gln Lys Gln Glu 3285 | Gly Lys Met | ccg caa aaa agg Pro Gln Lys Arg 3290 | gaa taa ggg 9888 Glu OCH Gly 3295 |
| cga cac gga aat gtt gaa Arg His Gly Asn Val Glu 3300 | tac tca tac Tyr Ser Tyr 3305 | Ser Ser Phe Phe | aat att att 9936 Asn Ile Ile 3310 |
| gaa gca ttt atc agg gtt Glu Ala Phe Ile Arg Val 3315 | Ile Val Ser 3320 | OPA Ala Asp Thr 3325 | Tyr Leu Asn |
| gta ttt aga aaa ata aac Val Phe Arg Lys Ile Asr 3330 | aaa tag ggg Lys AMB Gly 3335 | ttc cgc gca cat Phe Arg Ala His 3340 | ttc ccc gaa 1003 Phe Pro Glu |

Figure 2N

| | Cys | | | Thr | | | | | Leu | | | | | taa OCH | | 10080 |
|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|---------------------|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|-------------------|--------------------|--------------------|-------|
| | | | Gly | | | | | Pro | | | | | | ser 3375 | | 10128 |
| _ | _ | Val | | | | _ | Thr | - | _ | | | Arg | | tca Ser | _ | 10176 |
| | Val | | | | | Pro | | | | | Pro | | | gcg Ala | | 10224 |
| Gln | cgg Arg 3410 | gtg Val | ttg Leu ' | gcg Ala | Gly | gtc Val 415 | ggg ggg | gct Ala | ggc Gly | Leu | act Thr 3420 | atg Met | cgg | cat His | cag Gln | 10272 |
| agc Ser 342 | Arg | ttg Leu | tac Tyr | OPA | gag Glu 430 | tgc Cys | acc Thr | ata Ile | Cys | ggt Gly 435 | gtg Val | aaa Lys | tac Tyr | cgc Arg | aca Thr 3440 | 10320 |
| gat Asp | gcg Ala | taa OCH | Gly | gaa Glu 445 | aat Asn | acc Thr | gca Ala | Ser | ggc Gly 450 | gcc Ala | att Ile | cgc Arg | His | tca Ser 3455 | ggc Gly | 10368 |
| tgc Cys | gca Ala | Thr | gtt Val 460 | ej aaa | aag Lys | ggc Gly | Asp | egg Arg 465 | tgc Cys | 999. Gly | cct Pro | Leu | cgc Arg 470 | tat Tyr | tac Tyr | 10416 |
| gcc Ala | Ser | tgg Trp 475 | cga Arg | aag Lys | GJA aaa | Asp | gtg Val 480 | ctg Leu | caa Gln | ggc Gly | Asp | taa OCH 485 | gtt Val | GJA BBB | taa OCH | 10464 |
| Arg | cag Gln 490 | ggt Gly | ttt Phe | ccc Pro | Ser | cac His . 495 | gac Asp | gtt Val | gta Val | Lys | cga Arg 500 | cgg | cca Pro | gtg Val | cc | 10511 |

Fig.3

clonetherapt.99B3:

VH sequence :

GAGGTGAAGCTTCTCCAGTCTGGAGGTGGCCTGGTGCAGCCTGGAGGATCCCTGAAACT CTCCTGTGCAGCCTCAGGAATCGATTTTAGTAGATACTGGATGAGTTGGGTTCGGCGGG CTCCAGGGAAAGGACTAGAATGGATTGGAGAAATTAATCCAGATAGCAGTACAATAAAC TATGCACCATCTCTAAAGGATAAATTCATCATCTCCAGAGACAACGCCAAAAATACGCT GTACCTGCAAATGAGCAAAGTGAGATCTGAGGACACAGCCCTTTATTACTGTGCAAGAG GACTGGGACAGAACTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA

VL sequence :

Fig.4

clonetherapt.88E10 :

VH sequence :

GAGGTGAAGCTGGTGGAGTCTGGAGGAGGCTTGGTACAGCCTGGGGGTTCTCTGAGTCT
CTCCTGTGCAGCTTCTGGATTCACCTTCACTGATTACTCCATGAACTGGGTCCGCCAGC
CTCCAGGGAAGACACTTGAGTGGTTGGCTTTTATTAGAAACAAAGCTAATGGTTACACA
GCAGAGTACAGTGCATCTGTGAAGGGTCGGTTCTCCATCTCCAGAGATAATTCCCAAAG
CATCCTCTATCTTCAAATGAATGCCCTGAGAGCTGAGGACAGTGCCACTTATTACTGTG
CAAGGGGATGGTATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA

Fig.5

clonetherapt.152C3:

VH sequence :

GAGGTTCTGCTGCAGCAGTCTGTGGCAGAGCTTGTGAGGCCAGGGGCCTCAGTCAAGTT
GTCCTGCATAGTTCTGACTTCAACATTAAACACACCTATATGCACTGGGTGAAACAGA
GGCCTGATCAGGGCCTGGAGTGGATTGGAAGGATTGATCCTGCGAATGGTAAAACTATA
TATGCCCCGACGTTCCAGGGCAAGGCCACTATAACTGCGGACACATCCTCCAACACAGC
CTACCTGCATTTCAGCAGCCTGACATCTGAGGACGCTGCCATCTATTACTGTGCTAGAG
CTGGGGCTGGCTACTTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA

VL sequence :

GACATCTTGCTGACTCAGTCTCCAGCCATCCTGTCTGTGAGTCCAGGAGAAAGAGTCAG
TTTCTCCTGCAGGGCCAGTCAGAACATTGGCACAAGTATTTACTGGTATCAGCAAAGAA
CAAATGGTTCTCCAAGGCTTCTCATAAAGTATGTTTCTGAGTCTATCTCTGGGATCCCT
TCCAGGTTTAGTGGCAGTGGATCAGGGACAGAGTTTACTCTTAGCATCAACAGTGTGGA
GTCTGAAGATATTGCAGATTATTACTGTCAACAAAGTCATAGTTGGCCGCTCACGTTCG
GTGCTGGGACCAAGCTGGAGCTGAAA

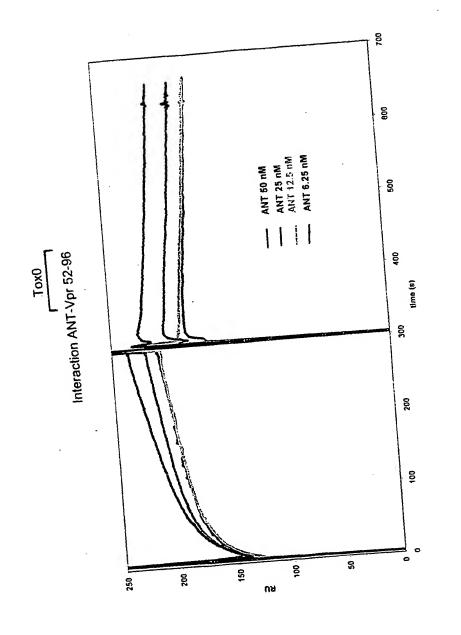
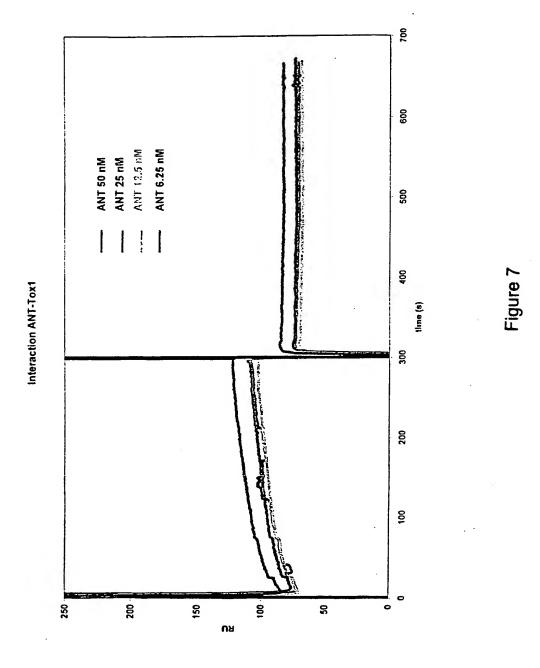
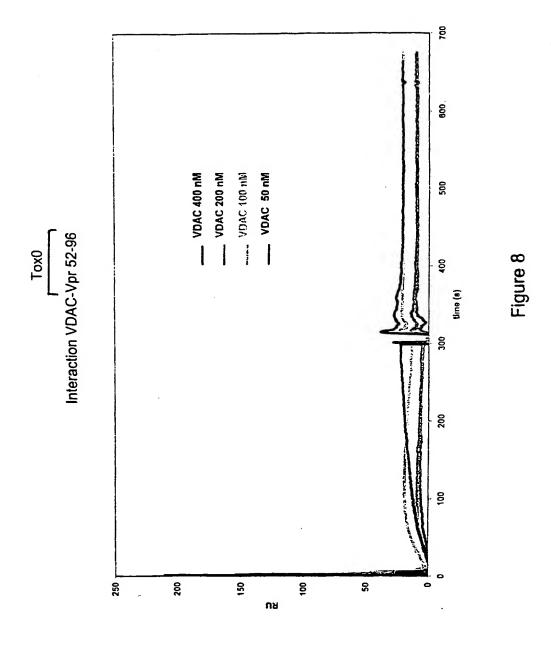
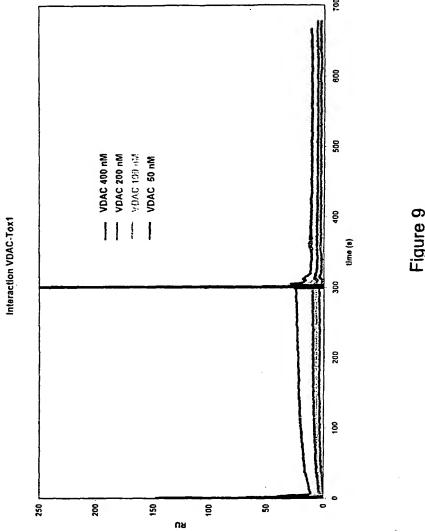


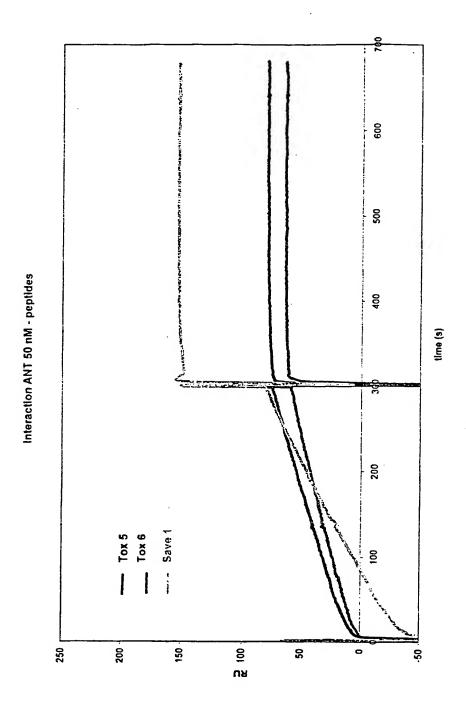
Figure 6



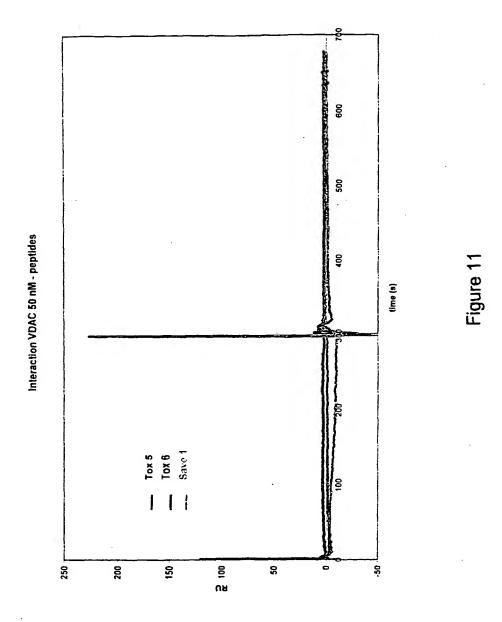


SUBSTITUTE SHEET (RULE 26)





-igure 10



SUBSTITUTE SHEET (RULE 26)

Second Step:

Figure 12: Obtention of the VH/VL chimeric DNA

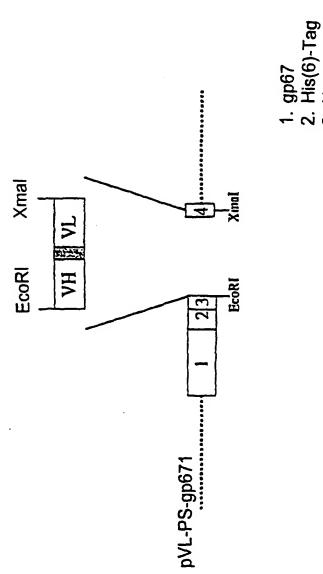


Figure 13: Map of the ScFv transfert vector